REMARKS

The present invention relates to novel cancer vaccines. More particularly, the invention relates to vaccines that include hapten-modified tumor cells for treating melanoma, and using the vaccines in a melanoma cancer patient thereby providing a therapeutic benefit.

Claims 1, 2, and 21-33 are currently pending. Claims 1 and 26 are amended herein as in the previously filed response, and claims 3-20 were canceled in a previous amendment. Claims 32 and 33 are added here again in response to the Examiner's rejection to the previous Amendment. No new matter is added by way of this Amendment.

Rejections

(1) The Examiner stated in the Office Action that the Amendment filed November 18, 2005 was improper for not complying with 37 C.F.R. 1.173(b).

(2) The Examiner stated in the Office Action that the Oath/Declaration under 37 C.F.R. §1.175 is defective.

(3) Claims 26-31 stand rejected by the Examiner under 35 U.S.C. §103 as being unpatentable over Berd, et al. (Proc. Amer. Assoc. Cancer Res., March 1989; 30:382 Abstract #1515; "Berd 1989") in view of Berd (Cancer Investigation, 1988; 6(3):337-349; "Berd 1988").

(4) Claims 26-31 stand rejected by the Examiner as being unpatentable over Berd et al. (Proc. Amer. Assoc. Cancer Res. March 1990; 31:279, Abstract #1654; "Berd 1990") in view of Berd 1988.

(5) Claims 26-31 stand rejected by the Examiner as being unpatentable over Murphy et al. (Lab. Invest., 1990, 62(1):70A, Abstract #412; "Murphy") in view of Berd 1988.

(6) Claims 2 and 21-25 stand rejected by the Examiner as being unpatentable over Berd 1989 in view of Berd 1988 and Fujiwara (J. Immunol. 1980, 124:863-869; "Fujiwara").

(7) Claims 2 and 21-25 stand rejected by the Examiner as being unpatentable over Berd 1990 in view of Berd 1988 and Fujiwara.

(8) Claims 2 and 21-25 stand rejected by the Examiner as being unpatentable over Murphy in view of Berd 1988 and Fujiwara.

(9) Claims 1 and 32 stand rejected as being unpatentable over Berd 1989 in view of Fujiwara.

(10) Claim 1 and 32 stand rejected as being unpatentable over Berd 1990 in view of Fujiwara.

(11) Claim 1 and 32 stand rejected as being unpatentable over Murphy in view of Fujiwara.

Responses

In response to rejection (1), the Applicant submits a new amendment for the Examiner's consideration. The Applicant respectfully requests that this objection be withdrawn.

In response to rejection (2), the Applicant submits herewith a new Declaration which corrects the defects cited by the Examiner in the previous Declaration. The Applicant respectfully requests that this rejection be withdrawn. In the event that the present Declaration is not sufficient, the Applicant requests that the Examiner inform the undersigned attorney as soon as possible.

In response to rejections (3) through (11), the Applicant presents the following arguments to the Examiner.

The three-prong test which must be met for a reference or a combination of references to establish a *prima facie* case of obviousness has not been satisfied in any of the §103 rejections asserted by the Examiner. The MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

At least one of these criteria has not been met in each of rejections (3) to (11).

With regard to rejections (3) to (5), the Examiner states that the combination of Berd 1989, Berd 1990, or Murphy with Berd 1988 renders claims 26-31 obvious because each of Berd 1989, Berd 1990, and Murphy teaches a method of treating melanoma patients with cyclophosphamide (CY) followed by autologous vaccine to induce delayed-type hypersensitivity (DTH) to melanoma cells. The Examiner further states that the method taught in these references includes administering low dose CY, and injecting patients with a vaccine of 10-25x10^6 autologous, irradiated melanoma cells mixed with BCG. The Examiner recognizes that Berd 1990 does not teach mixing the vaccine with BCG, but argues that doing this would have

been obvious to one of skill in the art in order to enhance the effect of the vaccine. The Examiner states that Berd 1988 teaches administration of the vaccine in three sites on the upper arm or leg, and that it would have been obvious for a skilled person to use the method taught in Berd 1989, Berd 1990, or Murphy in conjunction with the three-site administration on the upper arm or leg. Finally, the Examiner states that the recitation that the vaccine should induce a DTH response against unmodified melanoma cells is considered to be an inherent property of the vaccine.

The Examiner states that the Applicant's arguments in the previous response were not persuasive, and states that the only difference between the cited references and the claimed invention is that the cited references do not disclose injection of the vaccine at 3 sites on the patient's arm or leg. The Applicant respectfully disagrees with the Examiner, and maintains that the Examiner has not met the burden of proving a *prima facie* case of obviousness because there is no motivation or suggestion to combine these references nor is there any reasonable expectation of success if the references are combined. In addition, the Applicant maintains that the Examiner has used impermissible hindsight to combine the teachings of the cited references.

"Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999). "Particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). In the present Office Action, the Examiner has not demonstrated how a skilled artisan would select the elements of Berd 1989, Berd 1990 or Murphy and Berd 1988 and combine them in the manner claimed.

Berd 1989, Berd 1990 and Murphy teach use of haptenized tumor cells in a vaccine for treatment of melanoma. Berd 1988 teaches the use of non-haptenized tumor cells in a vaccine for treatment of melanoma. There is nothing in any of Berd 1989, Berd 1990 or Murphy that would motivate or suggest to one of skill in the art to combine the teachings of each of these references with Berd 1988. More specifically, there is nothing in any of these references that would teach or suggest to a skilled person that use of haptenized cells would work in combination with the method disclosed in Berd 1988 as an effective treatment for melanoma. A person of skill in the art, armed with the disclosure of Berd 1988 would not be motivated to use

the method taught in Berd 1988 with a vaccine that uses haptenized tumor cells. There is nothing in Berd 1988 that would indicate to one of skill in the art that the method taught in the reference would work with a vaccine that comprises haptenized tumor cells. For these reasons, the Applicant respectfully requests that rejections (3) to (5) be withdrawn by the Examiner.

Regarding rejections (6), (7), and (8), the Examiner states that claims 2 and 21-25 stand rejected in view of the combination of Berd 1988 and Berd 1989, or Berd 1988 and Berd 1990 with Fujiwara, or Berd (1988), Murphy (1990) and Fujiwara. The Examiner states that Fujiwara teaches conjugation of TNP to tumor cells and the use of TNP-conjugated tumor cells in treatment of tumors. The Examiner further argues that one of skill in the art would have expected that TNP-conjugated melanoma cells could be substituted for DNP-conjugated melanoma cells in order to treat melanoma.

The Examiner states that the Applicant's arguments in the previous response were not considered persuasive, and the Examiner asserts that Fujiwara teaches that TNP-conjugated tumor cells generate an immune response and enhance the rejection of tumor cells. The Applicant respectfully disagrees with the Examiner's assertion.

In response to rejections (6), (7), and (8), the Applicant respectfully reiterates that the Examiner has not met the burden of proving a *prima facie* case of obviousness because there is no motivation or suggestion to combine the stated references and because there is no expectation of success in treatment of melanoma with a TNP-modified vaccine. Berd 1988, Berd 1989, and Berd 1990 relate only to DNP-modified human melanoma cells, while Fujiwara relates only to TNP-modified mouse LSTRA (leukemia) or plastmacytoma tumor cells. The tumor cells are different, and the hosts from which the cells are derived and into which the vaccines are injected are of a different species.

There is no teaching or suggestion in any of Berd 1988, Berd 1989, or Berd 1990 that any other hapten is useful for modifying melanoma cells to treat melanoma. In addition, none of the references provides any expectation of success to make or use a TNP-modified human melanoma tumor cell vaccine to treat melanoma. Likewise, there is nothing in Fujiwara that teaches or suggests haptenizing melanoma cells to treat melanoma. Further, in order to elicit a strong response, the treatment method in Fujiwara requires pre-treatment of a mouse with TNP-modified proteins to prime the mouse to generate hapten-reactive amplifier cells, followed by immunizing the mice with hapten-coupled tumor cells (p. 867, second column, first paragraph).

None of Berd 1988, Berd 1989, or Berd 1990 teach priming a human patient to produce hapten-reactive amplifier cells. It is again asserted that the Examiner has used impermissible hindsight to combine these references to arrive at the present invention. The Applicant contends that the Examiner has not demonstrated how a skilled artisan would select the elements of Berd 1989, Berd 1990 or Murphy and Berd 1988 and combine them in the manner claimed.

In addition, the Applicant disagrees with the Examiner's statement that Fujiwara applies to any type of tumor cell. Fujiwara makes a general statement that a TNP-conjugated tumor cell may generate an immune response and enhance the rejection of tumor cells; however, Fujiwara does not provide any data for or otherwise support this conclusion for any other type of tumor cell except mouse leukemia and plastmacytoma derived from mice. Therefore, the Applicant asserts that Fujiwara does not enable any other type of tumor cell. For these reasons, the Applicant respectfully requests that the Examiner withdraw rejections (6), (7), and (8).

Claim 1 stands rejected by the Examiner in rejections (9) to (11) for being unpatentable over the combination either Berd 1989, Berd 1990, or Murphy with Fujiwara.

The Examiner states that the Applicant's arguments in the previous response were not considered persuasive, and the Examiner asserts that Fujiwara teaches that TNP-conjugated tumor cells generate an immune response and enhance the rejection of tumor cells. The Applicant respectfully disagrees with the Examiner's assertion.

In response to rejections (9) to (11), the Applicant reiterates that the Examiner has not met the burden of proving a *prima facie* case of obviousness because there is no motivation or suggestion to combine these references and because there is no expectation of success, even if the references are combined. There is nothing in Berd 1989, Berd 1990, or Murphy that would incline one of skill in the art to modify these references or combine them with Fujiwara. Berd 1989, Berd 1990, and Murphy relate only to DNP-modified human melanoma cells, while Fujiwara relates only to TNP-modified mouse LSTRA (leukemia) or plastmacytoma tumor cells. The Applicant further argues that there is nothing in Fujiwara that teaches or suggests haptenizing melanoma cells to treat melanoma. Likewise, there is no teaching or suggestion in any of Berd 1989, Berd 1990, or Murphy that any other hapten is useful for modifying melanoma cells to treat melanoma. In addition, none of the references provide any expectation of success to make or use a TNP-modified human melanoma tumor cell vaccine to treat melanoma. In addition, the Applicant points out that Fujiwara does not provide any data for or otherwise

support this conclusion for any other type of tumor cell except mouse leukemia and plastmacytoma derived from mice. Therefore, the Applicant asserts that Fujiwara does not enable any other type of tumor cell. For these reasons, the Applicant respectfully requests that the Examiner withdraw rejections (9) to (11).

Summary

The Applicant respectfully submits that each rejection of the Examiner to the claims of the present application has been either overcome or is now inapplicable, and that each of claims 1, 2, and 21-33 is in condition for allowance. Reconsideration and allowance of each of these claims are respectfully requested at the earliest possible date.

Respectfully submitted,
DAVID BERD

30 June 2006
(Date)

By: _____

Gail H. Griffin
Registration No. 51,941
Louis W. Beardell, Jr.
Registration No. 40,506
MORGAN, LEWIS & BOCKIUS, L.L.P.
1701 Market Street
Philadelphia, PA 19103
Telephone: (215) 963-5000
Direct Dial: (215) 963-5265
Facsimile: (215) 963-5001
E-Mail: ggriffin@morganlewis.com
Attorney for Applicant

GHG

Enclosures (Request for Continued Examination; Reissue Declaration; and Petition for three-month extension of time and associated fee)